REMARKS

Status of the Claims

Claims 1, 2, 5-9, 11, 14, 15 and 18-21 are pending, with claims 1 and 21 being independent. Claims 2-5, 10-14 and 16-20 are canceled herein without prejudice or disclaimer thereto. Applicants reserve the right to file at least one continuation application directed to any subject matter canceled by way of the present Amendment. Claims 1, 9, 15, and 21 are amended herein. Support for the claim amendments can be found throughout the specification and claims as filed, including at claims 3-5. As such, no new matter has been added.

Applicants respectfully request the Examiner to reconsider and withdraw the outstanding rejections in view of the foregoing amendments and the following remarks.

Priority

Applicants note with appreciation that the Office acknowledges receipt of the papers relating to priority pursuant to 35 U.S.C. § 119(a)-(d).

Claim Rejections Under 35 U.S.C. § 112, second paragraph

Claims 6, 11, 14, and 19 stands rejected under 35 U.S.C. § 112, second paragraph, for the recitation of "is comprised between". Claim 6 is amended herein to replace this phrase with "is between".

Claims 9 and 20 stand rejected under 35 U.S.C. § 112, second paragraph, for the recitation of "is administrable via the oral or the parenteral route". Claim 20 is canceled herein without prejudice or disclaimer. Claim 9 is amended herein to recite "in a standard form adapted to administration via the oral or the parenteral route."

Accordingly, these rejections should be withdrawn.

Claim Rejections Under 35 U.S.C. § 103

Claim 1-2, 5-9, 11, 14-15, 18-19 and 20-21 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Brulls (U.S. Patent No. 6,730,685) in view of Mangel (WO 01/56573). Applicants respectfully traverse.

Before turning to the cited references, Applicants note that the present invention provides a pharmaceutical composition with anti-inflammatory properties which treats the symptoms of pain and inflammatory diseases, while avoiding the adverse side effects associated with the use of anti-inflammatory agents. The present invention provides a treatment for pain and inflammation. The present invention further treats the symptoms of inflammatory diseases (such as inflammatory rheumatism, arthritis and osteoarthritis), by preventing or adverse effects causing gastro-duodenal lesions and peptic ulcers.

The present claims are directed to a pharmaceutical composition comprising an anti-inflammatory agent selected from a nonsteroidal anti-inflammatory agent (NSAID) or a cyclooxygenase-2 inhibitor, in combination with tenatoprazole. The NSAID may be aspirin, diclofenac, etodolac, indometacin, naproxen, ibuprofen or piroxicam. The cyclooxygenase-2 inhibitor may be rofecoxib and celecoxib.

The adverse effects associated with the use of anti-inflammatory agents can be severe and unpredictable, particularly in high-risk subjects such as elderly. The concomitant administration of a standard proton pump inhibitor does not fully meet the need for preventive therapy. The present invention addresses this problem.

As discussed in the specification, studies performed with the present invention show that the combination of tenatoprazole and an anti-inflammatory agent selected from those

recited in the presently amended claim 1 achieves unexpected benefits and uses when compared with other PPIs and with anti-inflammatories used alone or in combination.

The specific combination as claimed herein allows for the control of gastric acidity, along with an anti-inflammatory activity which provides improved efficacy and better safety than known therapies. These advantages result from a specific tenatoprazole activity which complements that of the claimed anti-inflammatory agents, and which is not exhibited by other proton pump inhibitors.

As shown on pages 6-8 of the present specification, tenatoprazole differs from other PPIs in its much longer elimination half-life, and also in its considerable degree of tissue exposure. The pharmacokinetics studies performed show that tenatoprazole exhibits a long half-life and high AUC values (area under the curve), providing evidence of a low rate of metabolism and/or high bioavailability. Accordingly, the prolonged exposure linked to the long elimination half-life of tenatoprazole, and demonstrated by the AUC value, allows tenatoprazole to remain at the site of activity in the body for a much longer time than other PPIs, and thus provides a pharmacodynamic effect which is prolonged over time.

Experiments have shown that tenatoprazole is endowed with a plasma half-life/ pump regeneration time ratio which is notably higher than that seen with other PPIs , thus permitting its use in pathologies where currently available medicinal products have little effect. It can be particularly useful in treating the nocturnal symptoms of gastroesophageal reflux and gastro-duodenal ulcers.

Therefore, when it is combined with one of the anti-inflammatory agents recited in the present claims, tenatoprazole, as compared with other PPIs, provides significant advantages with respect to suppressing gastric acidity. This combination allows effective action on the nocturnal peak of gastric acidity and on nocturnal symptoms in patients suffering from

gastroesophageal reflux, in which it achieves marked relief, even in patients refractory to classic therapies with standard PPIs such as omeprazole. These particular properties of tenatoprazole were unexpected and not known from the prior art at the time the invention was made. These benefits are certainly not disclosed in the cited references.

Brulls discloses formulations that comprise a water free or almost water free polyethylene glycol solution of sodium or potassium salt of a PPI derived from benzimidazole. These formulations are useful for inhibiting gastric acid secretion in mammals. Brulls recites a list of 10 compounds among which tenatoprazole is mentioned at the top of column 5. However, nothing in Brulls indicates that tenatoprazole is somewhat preferred or exhibits particular properties over other PPIs. On the contrary, in all of the examples provided by Brulls, the formulations have been prepared using omeprazole.

Further, Brulls fails to disclose any particular NSAID or any particular combination of one PPI with a NSAID. Brulls indicates that PPIs can be associated with other drug treatments such as one or more antibacterial compounds, a motility stimulating drug, an anti-acid and/or H2-blockers, such as for instance ranitidine (col. 7, lines 22-26). Accordingly, upon review of Brulls, the skilled artisan would prefer the use of omeprazole, alone or in combination with other drugs such as NSAIDs, antibacterial compounds, motility stimulating drugs, anti-acids and/or H2-blockers.

Mangel does not remedy Brulls. Mangel discloses anti-inflammatory agents of the COX2-inhibitors series which are likely to increase the gastro-intestinal motility. Among the very numerous compounds listed in this document, celecoxib and rofecoxib are mentioned, for example at page 5, lines 7-8. Mangel also indicates that COX-2 inhibitors can be administered in combination with one or more other therapeutic agent(s) and mentions as examples different categories of drugs such as PPIs (page 8, lines 15-17). In this list

omeprazole is mentioned in the first position while tenatoprazole is cited at the final end of the list. However, the examples do not disclose any combination of a COX2-inhibitor with a PPI.

Therefore, even if the one skilled in the art had combined the teaching of Brulls and Mangel, they would not arrive at the claimed invention.

Claims 1-2, 5-7, 9, 11, 14-15, 18-19 and 20-21 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Chih-Ming (WO 02/22108) in view of Mangel and Naesdal (*European Journal of Gastroenterology and Hepatology,* 2001, 13:1401-1406).

Chih-Ming discloses a solid composition comprising a NSAID extended release tablet and an enterically coated proton-pump inhibitor without a separating layer between the PPI and the enteric coat. As discussed in the present specification, this type of combination as disclosed in Chih-Ming does not provides a specific combination of active ingridients but instead provides a new dosage form. Among NSAIDs, only diclofenac is mentioned by Chih-Ming and amoung PPIs, only omeprazole is mentioned. Tenatoprazole is not disclosed at all. Naesdal also fails to disclose tantoprazole, as the only disclosed PPI is omeprazole.

Therefore, even if the one skilled in the art had combined the teaching of Chih-Ming, Mangel and Naesdal, they would not arrive at the claimed invention. Instead, the skilled artisan would pursue a therapy containing omeprazole.

Claims 1-2, 5-9, 11, 14-15, 18-19 and 20-21 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Chih-Ming in view of Mangel and in further view of Bergstrand (U.S. Patent No. 5,753,265).

Bergstrand does not cure the deficiencies of Chih-Ming, Mangel, and Naesdal, as discussed above. Bergstrand discloses pharmaceutical compositions containing a PPI and lists different compounds, including tenatoprazole. There is no mention at all of the newly

discovered unexpected phramcokinetic properties of tenatoprazole. Tenatoprazole is not mentioned as a preferred compound and is not used in the formulation examples. Accordingly, there is no motivation to combine tenatoprazole with one of the anti-inflammatory agents recited in amended claim 1.

In light of the above, Applicants respectfully request that the rejections under 35 U.S.C. § 103 be withdrawn.

CONCLUSION

If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #104006.B130121).

Respectfully submitted,

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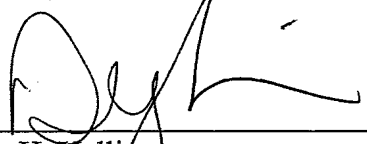

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